(Molecular) epidemiology of HIV-1, HIV-2 and HTLV-1 in Guinea-Bissau
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Citation for published version (APA):
van Tienen, C. (2011). (Molecular) epidemiology of HIV-1, HIV-2 and HTLV-1 in Guinea-Bissau

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Chapter 10

Discussion
HIV-2 and HTLV-1 are neglected tropical infections

In sharp contrast to HIV-1, HIV-2 and HTLV-1 are not well known and have raised relatively little scientific attention. In an abstract by Verdonck et al. at the 15th International Conference on Human Retroviruses: HTLV and Related Viruses, this was quantified by examining the number of publications on HTLV-1: this was low and did not increase between 2001 and 2010 [1]. A search for HIV-2 publications gave very similar results (both HIV-2 and HTLV-1 <750 publications per 5-year period and no increase over the last 10 years), while HIV-1 led to more than 16,000 publications per 5-year period and the number was increasing over the past 10 years (Figure 1). With an estimated 34 million people with HIV-1 infection in 2010 and a very high associated morbidity and mortality, the disease burden of HIV-1 is much larger than that of HIV-2 and HTLV-1. However, because much less is known about the prevalence, morbidity and mortality of HIV-2 and HTLV-1, the burden of disease due to these infections is more difficult to estimate. No up-to-date estimates exist for the number of people infected with HIV-2 or HTLV-1 [2].

For HIV-1, improved anti-retroviral treatment (ART) and huge efforts to improve access to ART in sub-Saharan Africa have led to more than 5 million people currently taking ART [3]. Successful ART leads to mortality rates of HIV-1 infected patients similar to those of age- and sex matched uninfected individuals in sub-Saharan Africa [4]. Large randomized controlled trials have been conducted to optimize treatment strategies for HIV-1. Some of the classes of antiretroviral drugs developed to treat HIV-1 are known to be effective against HIV-2 as well. However, no randomized controlled trials of treatment regimens against HIV-2 infection have been conducted [5], and the treatment of HIV-2 infection is not evidence-based. To date there is no effective treatment for HTLV-1 infection [6]. A call for treatment trials for Tropical Spastic Paraparesis (TSP) was made at the 15th International Conference on Human Retroviruses: HTLV and Related Viruses by Fabiola Martin [7]. Jorge Casseb argued that TSP should be listed as a neglected disease because of the large number of people infected worldwide, the low awareness of the disease amongst health care workers and because no effective treatment is available [8].

The journal *Plos Neglected Tropical Diseases* defines its field of interest as follows: “The Neglected Tropical Diseases are defined as a group of poverty-promoting chronic infectious diseases, which primarily occur in rural areas and poor urban areas of low-income and middle-income countries. They are poverty-promoting because of their impact on child health and development, pregnancy, and worker productivity, as well as their stigmatizing features.” HTLV-1 and HIV-2 should be designated as tropical neglected infections – they do not generate disease in all infected individuals but clearly impact on all the above-mentioned health aspects. More attention and research are needed and one way of increasing the awareness may be by declaring these infections ‘neglected’ so more funding possibilities may become available.
HTLV-1 transmission

In chapter 8 we examined the hypothesis that young men could have acquired HTLV-1 during a traditional circumcision ceremony. The sequences from these young men were not identical to each other and did not cluster together significantly. Although this does not rule out non-sexual horizontal spread, in these young men this was probably not the case. Disturbing reports in the media on evidence that increasing drug trafficking is taking place in Guinea-Bissau also raises the question whether injecting drug use could contribute to the transmission. In Caio, based on personal communication and observation, this does not seem to be the case thus far. This transmission route should be taken into consideration though in future studies.

The finding of 2 people who were infected with HTLV-1 subtype g, clustering with the STLV-1 Tan90, drew attention to direct monkey-to-human transmission. The only report so far describing these sequences in humans concerned monkey hunters in Cameroon and these men were probably infected through hunting accidents, exposing them to monkey blood [9]. Especially since the HIV-1 pandemic, zoonoses are increasingly important. Emerging infectious diseases are increasing worldwide (between 1940 and 2004) [10]. Of these emerging infectious diseases, more than half were zoonoses and the majority of these originated from wildlife [10]. Little is known, though, about the exact interaction between animals and humans, which complicates the prevention of zoonoses [11]. In a model by Pike et al., 5 stages are described for an animal pathogen to become a human
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pathogen, defined by the transmission that occurs (only between animals, primary infections to humans only, limited human-to-human transmission, sustained human transmission and exclusive transmission between humans) [11]. We don't know in which stage HTLV-1 subtype g in Caio is. One way to gain information on the possibility of monkey-to-human transmission would be to measure the presence of Simian Foamy Virus (SFV) in the Caio (human) community, using this infection as a sensitive marker for naturally occurring, perhaps less transmissible simian retroviruses [12]. SFV infection was detected in 1% of a population of people in close contact with monkeys in Cameroon and phylogenetic analyses showed these SFV infections originated from different monkeys [12]. The further exploration of indeterminate samples, i.e. those with a positive ELISA but a negative PCR or Western Blot, would be a good starting point to explore potential other HTLV (sub)types.

Prevention of vertical transmission of HTLV-1

The risk of vertical transmission is high for HIV-1 (appr. 25 – 30%) and for HTLV-1 (appr. 25%) infection. Breastfeeding by HIV-1 infected mothers has been associated with an additional 4 – 22% transmission risk to the child [13-16]. However, the benefits of breastfeeding by HIV-1 infected mothers have been shown to outweigh the risks of not breastfeeding in settings in sub-Saharan Africa [17]. Evidence obtained so far (summarized by Humphrey) [17], suggests that for HIV-exposed infants in developing countries, avoidance of breast-feeding will not improve infection-free survival and could actually reduce survival. HIV-exposed infants in developing countries will probably benefit from exclusive breast-feeding for the first 6 months of life. Continued breast-feeding after that (for an as yet unknown duration), will provide the greatest chance of infection-free survival [17]. In the case of HTLV-1, transmission mainly takes place during prolonged breastfeeding and probably to a very minor extent during pregnancy and delivery. In Japan, introduction of advice of bottle feeding to HTLV-1 infected mothers led to a dramatic reduction in vertical transmission [18]. However, no trials have been conducted in resource-poor settings such as sub-Saharan Africa to identify a suitable approach to prevent vertical transmission of HTLV-1. Would prevention of HTLV-1 MTCT in developing countries be achievable? The only paper with a clear advice was a review published in 2010 by Mylonas et al., who propose a maximum of 3 – 6 months of breastfeeding by HTLV-1 infected mothers if bottle feeding is not possible due to ‘socio-economical circumstances’ [19]. Unfortunately, the authors do not give a clear rationale for this advice. The key question is whether the benefits of avoiding HTLV-1 infection outweigh the risks of not breastfeeding. HTLV-1 can cause Adult T cell Leukemia (ATL) or TSP in up to 5 – 10% of infected individuals and HTLV-1 infection acquired during childhood is associated with an even higher risk of ATL [20]. HTLV-1 infection, probably irrespective of the route of acquisition, is associated with increased mortality. Reports on mortality associated with HTLV-1 infection all report increased mortality rates compared to uninfected people (mortality rate ratios ranging from 1.1 to 3.8), though not all were statistically significant (Chapter 6) [21-
The reasons for this increased risk are not clear, but changes in immunity leading to a higher susceptibility or worse outcome of certain infections may be important. Associations of HTLV-1 with tuberculosis, HIV, hyperstrongyloidosis and different types of inflammation have been reported (reviewed in [24]). One paper suggests HTLV-1 infection could actually have a positive effect; HTLV-1 infected individuals had a lower chance of developing gastric cancer in a case-control study in Japan [25]. In a commentary, Blaser suggests the idea that this may be an example of ‘viral commensalism’, beneficial to the host [26]. However, not all confounding factors could be ruled out in this study and the results should be interpreted with caution.

On the other hand, the risks of early weaning should be taken into account. The promotion of breastfeeding (for 6 – 11 months) has been estimated to be the most effective strategy to prevent child mortality in resource limited settings [27] and WHO recommends at least 6 months of exclusive breastfeeding [28]. Also many studies investigating the vertical transmission of HIV-1 have clearly shown the benefits of breastfeeding [17]. Abrupt cessation of breastfeeding in resource poor settings did not improve HIV-free survival among children and was harmful to the HIV-infected children [29]. Although these findings cannot be simply extrapolated to HTLV-1 infection, they do suggest simply shortening the time of exposure to infected breast milk may not be the optimal strategy for prevention. The Bandim Health Project showed in several studies conducted in Guinea-Bissau that early weaning is associated with increased mortality and increased risk of diarrheal diseases among children [30-33]. Mylonas et al. suggest weaning at the age of 3 – 6 months [19]. Studies in various cohorts have shown that prolonged breastfeeding is associated with an increased risk of transmission, especially after 6 – 12 months of age [34-36] (incidentally, in Chapter 7 we were not able to demonstrate this, because in our study population all except one of the children was breastfed for more than 12 months) and avoiding breastfeeding can lead to a dramatic reduction in transmission [18]. A high proviral load is an (independent) risk factor as well [Chapter 7] [35-36]. A plausible biological explanation for this increasing risk over time is the decreasing level of maternal antibodies in the child’s blood to almost nil at 6 to 11 months after birth [35,37]. This waning of maternal antibodies coincides with an increase of transmission of HTLV-1 [35,37]. Thus, a mother’s high proviral load in combination with waning antibodies in the child leads to an increased risk of HTLV-1 transmission, especially after 6 – 12 months after birth. This would be an argument for cessation of breastfeeding at 6 – 12 months after birth, and not 3 – 6 months, as recommended by Mylonas et al. [19], if it should be advised at all. Thus, certainly in some resource-poor settings, such as Guinea-Bissau, the immediate risks of weaning at 6 months are likely to be more harmful to the child than the risk of acquiring HTLV-1 and the associated morbidity/mortality. This is likely to vary by country and will strongly depend on the exact socio-economic circumstances. Studies in developing countries are needed to further examine the possibilities of MTCT prevention.
HIV-2: leading HIV-1 by example?

Recently, a large trial in heterosexual couples who were discordant for HIV-1, revealed that transmission of HIV-1 could be reduced to virtually nil by treating the HIV-1 infected partner with ART [38]. This appears to support the idea that early treatment could halt the HIV-1 epidemic [39]. Although this is very promising, many more data and specific modelling are crucial to estimate what is needed to reduce the reproductive number (R₀) of HIV-1 below 1 [40]. A natural model for a declining HIV-1 epidemic may be the HIV-2 epidemic [41]. Many West African countries have now reported a substantial decrease in prevalence and incidence and it is thought HIV-2 is disappearing [42-44]. As Bruhn and Gilbert point out in their commentary, this is the goal for the early treatment of HIV-1 on a large scale [41]. The lower levels of viremia in HIV-2 infection have been shown to be associated with a much lower MTCT and sexual transmission than in HIV-1 infection [45-46]. The low level of viremia naturally present in many HIV-2 infected individuals would represent the HIV-1 patients on successful anti-retroviral treatment and would mimic the low risks of horizontal and vertical transmission. The exact causes for the declining HIV-2 epidemic should be explored by modelling to further shed light on this issue. Although there are limitation to such a comparison (e.g. the sex and age distribution of both infections are very different), the analyses from Chapter 9 of this thesis show that early infection is associated with higher onward transmission rates as has been shown for HIV-1 [47]. The comparison would only be applicable to the heterosexual HIV-1 epidemic, since this seems to be the most common form of transmission [48] (although homosexual transmission has been shown to contribute in neighbouring Senegal; studies in Guinea-Bissau are lacking) [49]. A difference between the epidemics is the relatively small number of HIV-2 infected persons compared to the number of HIV-1 infected persons. The advantage of these small numbers is that it may be feasible to obtain complete datasets and describe whole transmission networks in order to understand the declining epidemic [41].

A crucial question would be what percentage of a population would need to have undetectable viral loads to reduce R₀ below 1. This question is probably best answered by early data from the Caio cohort. Berry et al. described that 36% of HIV-2 infected persons had a viral load below 100 copies/ml [50]. In the study in 2003 (Chapter 4 of this thesis) this was similar, with 29% having an HIV-2 viral load below 100 copies/ml. A fairly straightforward approach would be to conduct a new survey in Caio to trace the epidemiological trends of HIV-1 and HIV-2. In this survey viral loads and CD4 counts or percentages of all infected individuals should be measured. This would help to determine the current proportion of elite controllers which could be used for modelling.

Recently, HIV-1 community viral load has been shown to positively correlate with changes in incidence and a same approach could be used to explore their use in HIV-2 [51]. Information on viral load and especially CD4 count/%) would be of great benefit to the (potential) patients as these have been shown to be better markers of mortality (and disease progression) in HIV-2 in a community.
setting (Chapter 4 of this thesis). People participating in the survey should be encouraged to obtain their HIV test results; few people came to hear their HIV results from the counsellor in past surveys and with the currently available ART, early treatment should be the aim.

References


Discussion


